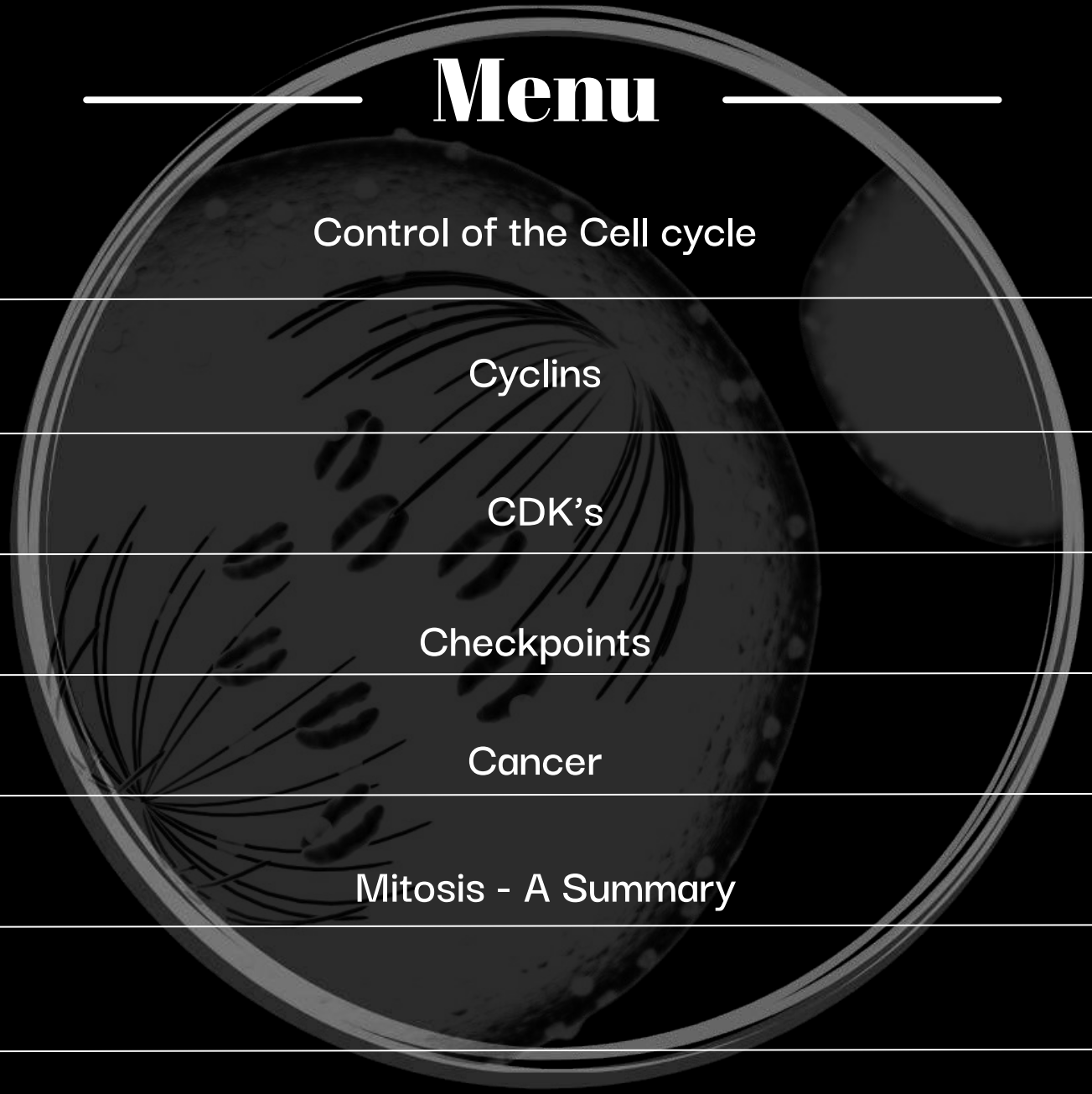
The Cell Cycle & Cancer

- *Know that the cell cycle is a repeating sequence of cellular growth and division during the life of an organism.*
- *Understand that cells divide to reproduce (in the case of a unicellular organism), to grow, and to replace worn out or damaged cells.*
- *Describe the stages of the cell cycle*
- *Know that the cell cycle in eukaryotes is controlled by proteins at three main checkpoints*
- *Recognize that if any of the genes necessary to make the proteins that regulate cell growth and division are mutated, the protein may not function, and the regulation of cell growth and division may be disrupted.*

MAMMOTH
SCIENCE

Menu

Menu

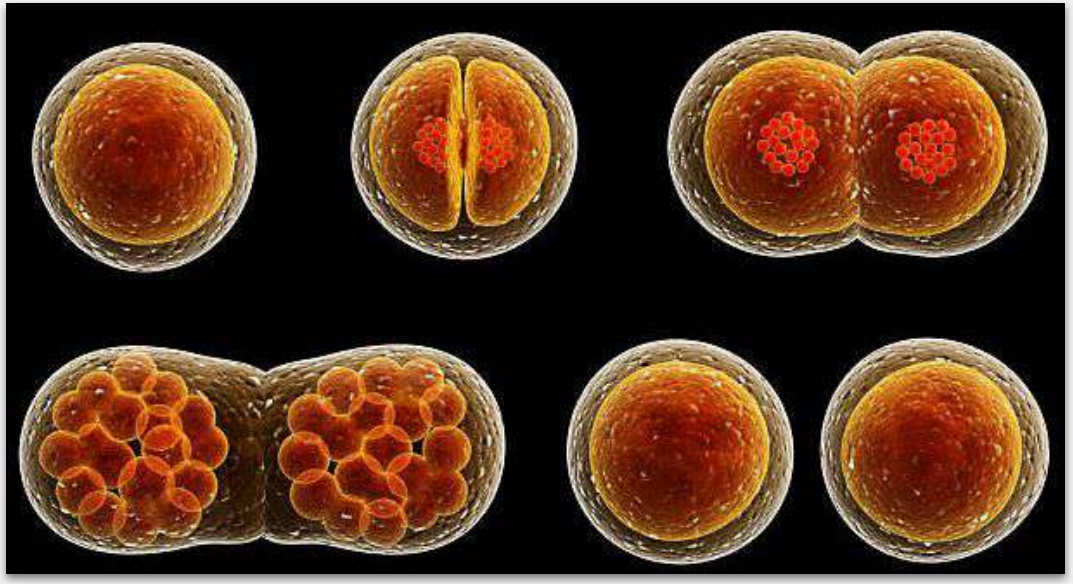


The Cell Cycle - Introduction

Introduction:

- All cells are derived from pre-existing cells
- New cells are produced for repair and to replace damaged or old cells
- Differs in Prokaryotes (bacteria - binary fission) and Eukaryotes (protists, fungi, plants, & animals)

Reasons for Cell Division



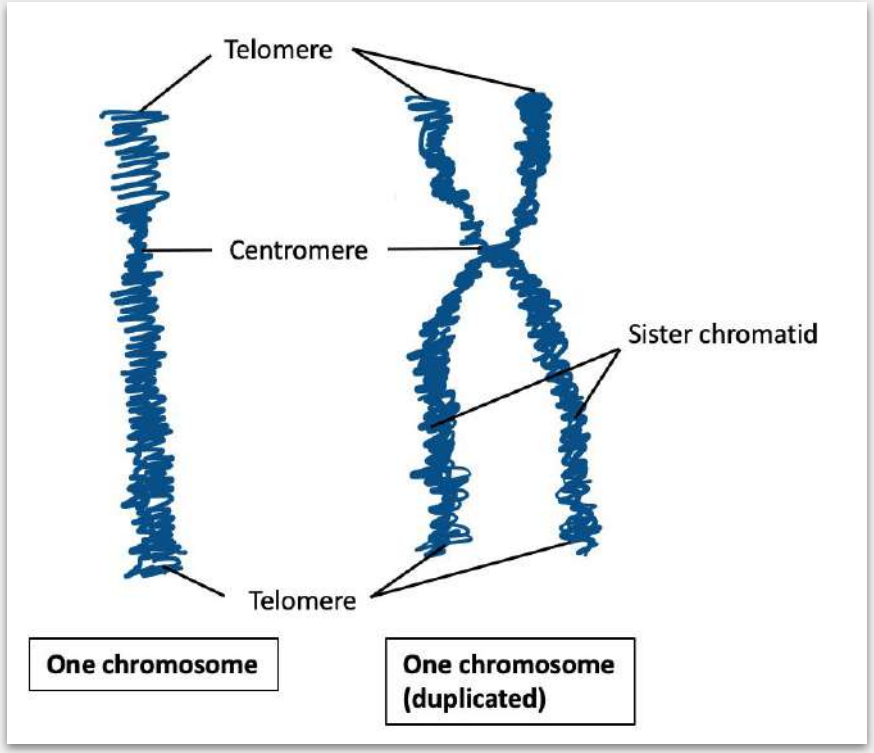
Reasons for Cell Division:

- **Cell Growth**
- **Repair** & **replacement** of damaged cell parts
- **Reproduction** of some species
- Why do cells need to replicate their genetic material (chromosomes) before they go through mitosis?
  - The instructions for making cell parts are encoded in the DNA, so each new cell must get a complete set of the DNA molecules
  - **DNA Replication:**
    - **DNA** must be **copied** or **replicated** **before** cell division
    - Each new cell will then have an **identical copy** of the **DNA**

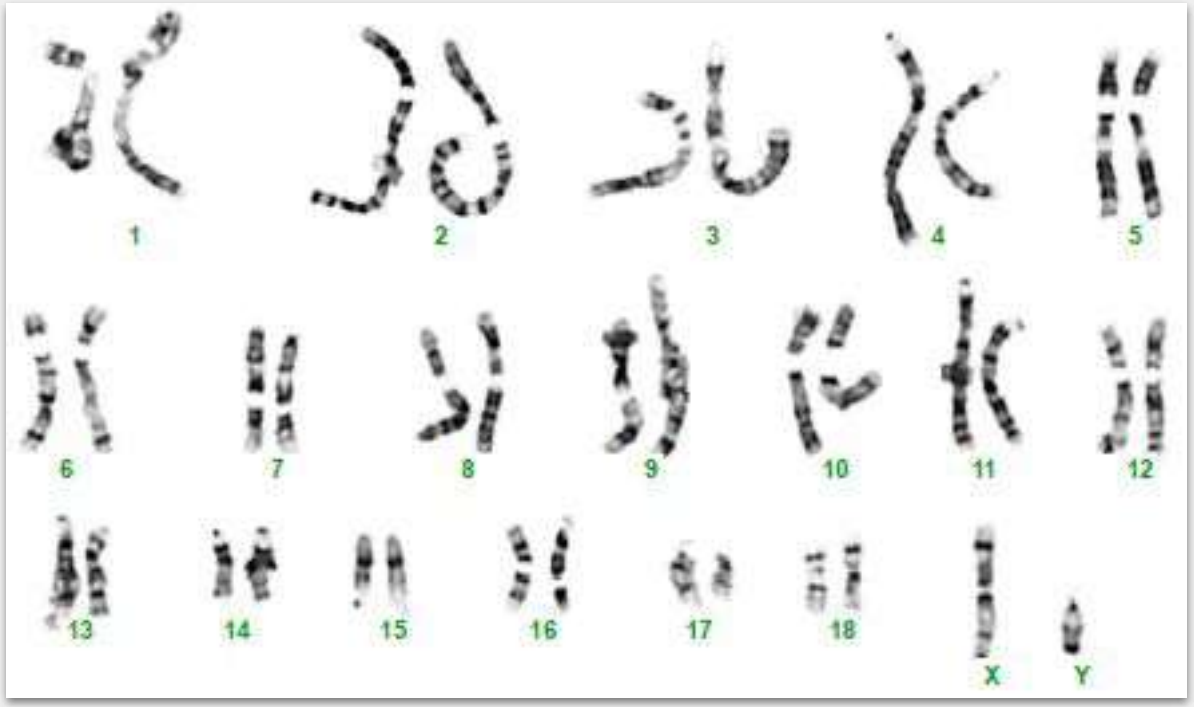
Chromosomes

Chromosomes

- Structure:
  - ➔ DNA is tightly coiled around proteins called histones. Further condensing forms a chromosome
- Replication:
  - ➔ When chromosomes replicate they go from one chromatid to two identical chromatids (called “sisters”) attached by the centromere.
  - ➔ When the chromatids are drawn apart toward opposite poles during Anaphase, the separated chromatids are now each called a chromosome.



Karyotype



Karyotype

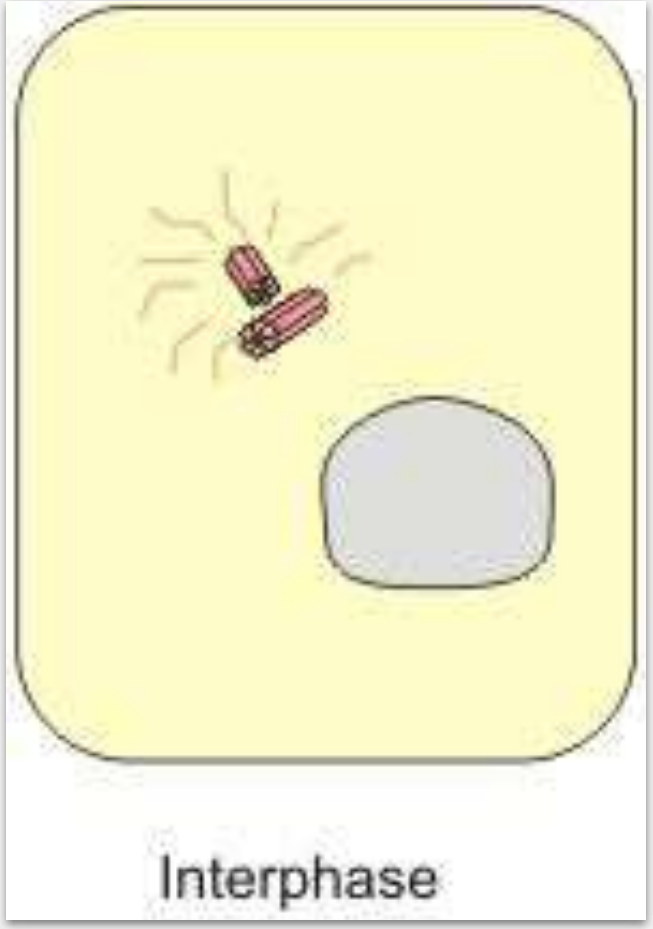
- ➔ A picture of the chromosomes from a human cell arranged in pairs by size
- ➔ First 22 pairs are called **Autosomes**
- ➔ Last pair are the **Sex Chromosomes**
- ➔ **XX female** or **XY male**
- ➔ Boy or Girl? The male parent & the ***Y chromosome*** decides

The Cell Cycle Summary - Interphase

The Cell Cycle

- Five Phases of the Cell Cycle:

1. **G1/ Gap 1 – Primary Growth Phase**
   - 1st growth stage after cell division
   - Cells **mature** by making **more cytoplasm & organelles**
   - Cell carries on its normal metabolic activities
2. **S – Synthesis Phase**
   - **DNA is copied** or **replicated**
3. **G2 / Gap 2 – Secondary Growth Phase**
   - 2nd Growth Stage
   - Occurs after DNA has been copied
   - All cell structures needed for division are made (e.g. **centrioles**)
   - Both **organelles** & **proteins** are **synthesized**



Mitosis

01

Mitosis - Overview

- ➔ Division of the nucleus
- ➔ Also called Karyokinesis
- ➔ Only occurs in Eukaryotes
- ➔ Has four stages
- ➔ Doesn't occur in some cells such as brain cells
- ➔ **Four Stages:**

02

Early Prophase

- ❑ **Early Prophase**
  - ➔ Chromatin in nucleus condenses to form visible chromosomes
  - ➔ Mitotic spindle forms from fibers in cytoskeleton or centrioles (animal)

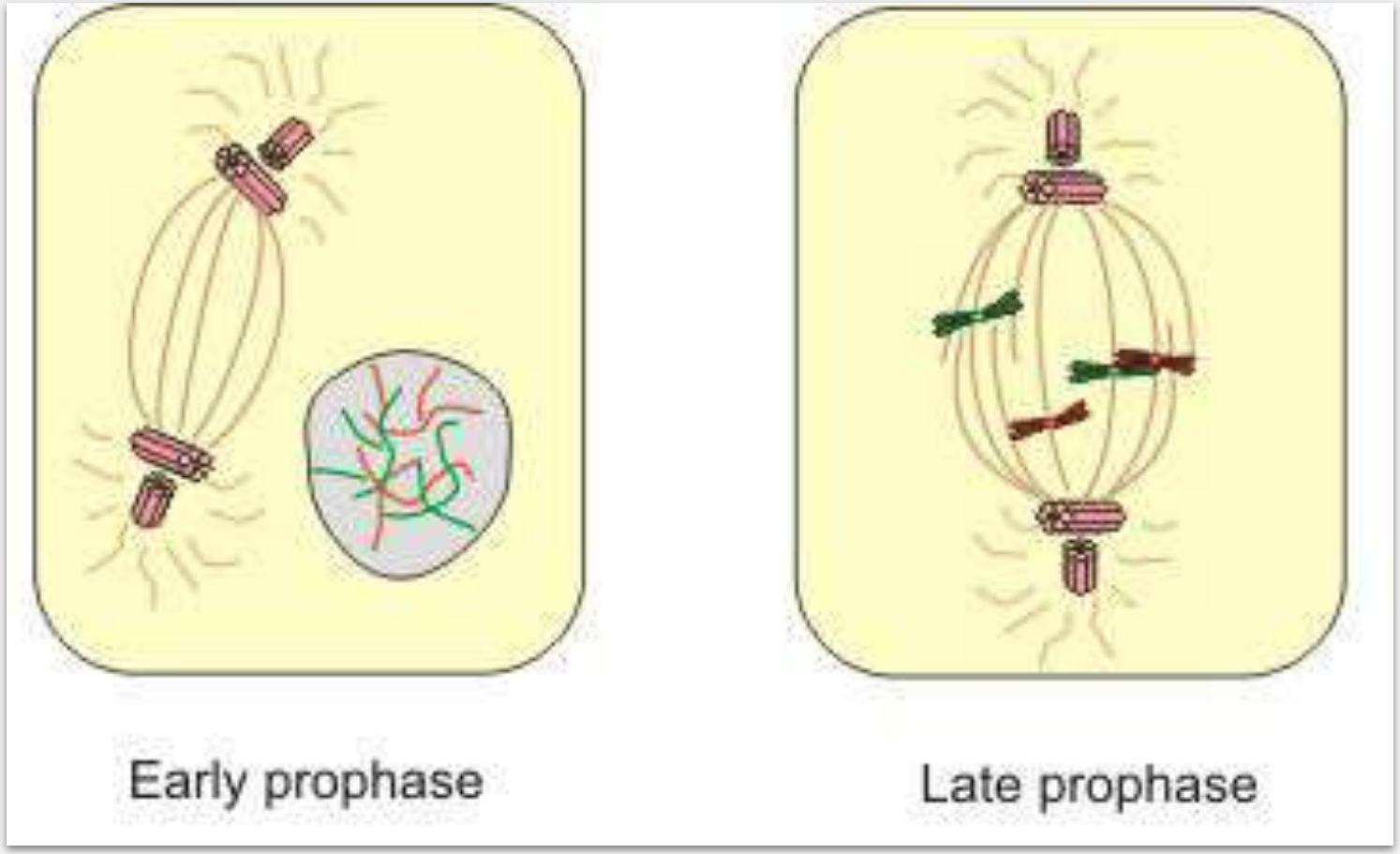
03

Late Prophase

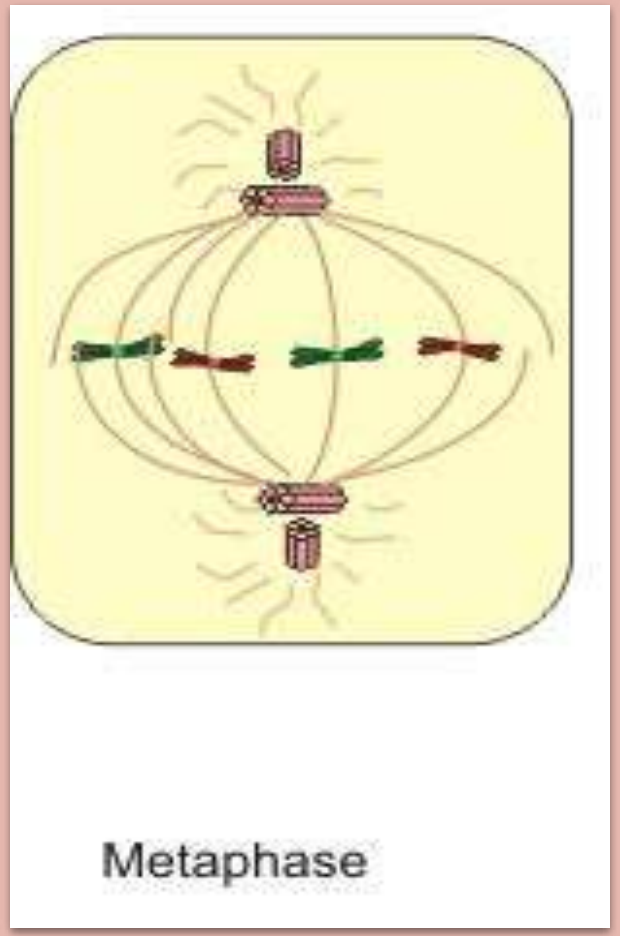
Late Prophase

- ➔ Nuclear membrane & nucleolus are broken down
- ➔ Chromosomes continue condensing & are clearly visible
- ➔ Spindle fibers called kinetochores attach to the centromere of each chromosome
- ➔ Mitotic Spindle finishes forming - The mitotic spindle forms from the microtubules in plants and centrioles in animal cells. Polar fibers extend from one pole of the cell to the opposite pole. Kinetochore fibers extend from the pole to the centromere of the chromosome to which they attach. Asters are short fibers radiating from centriole

Prophase - Early & Late



Metaphase



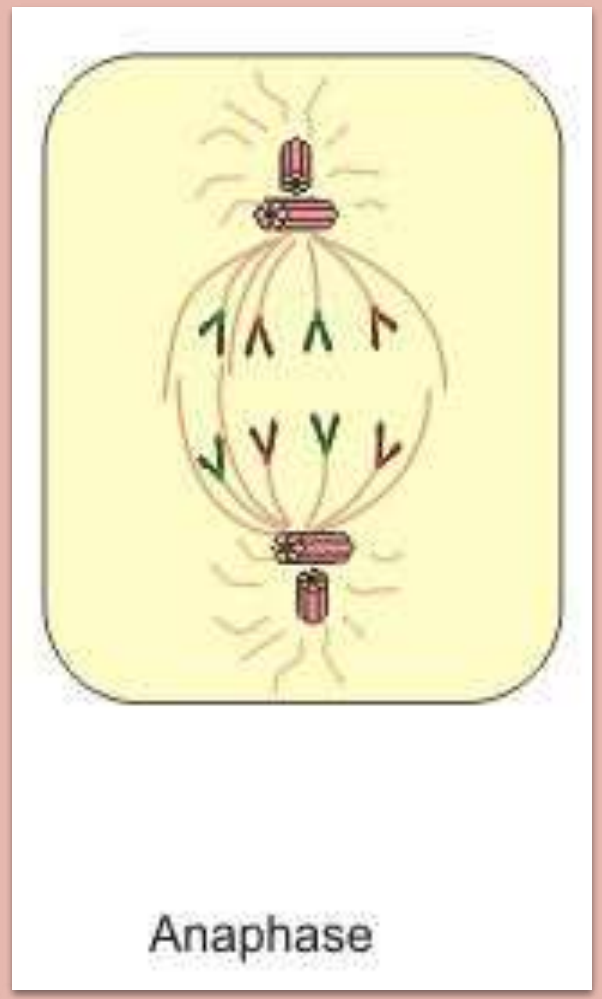
Metaphase

- ➔ Chromosomes, attached to the kinetochore fibers, move to the center of the cell
- ➔ Chromosomes are now lined up at the **equator / Middle**

Anaphase

Anaphase

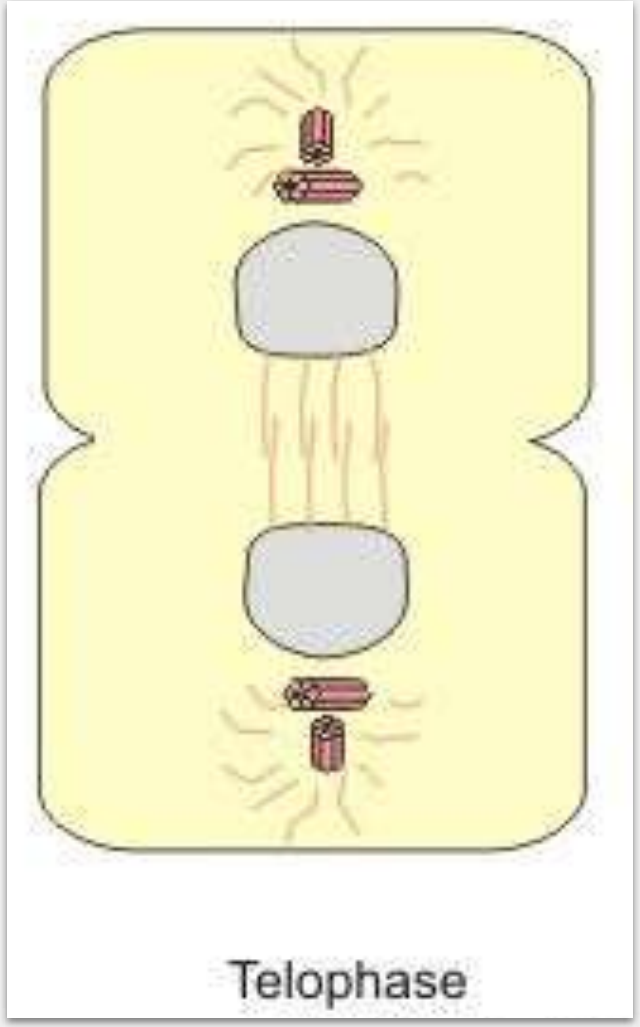
- ➔ Occurs rapidly
- ➔ Sister chromatids are **pulled apart** to opposite poles of the cell by shortening kinetochore fibers
- ➔ Polar Microtubules elongate preparing for cytokinesis



Telophase

Telophase

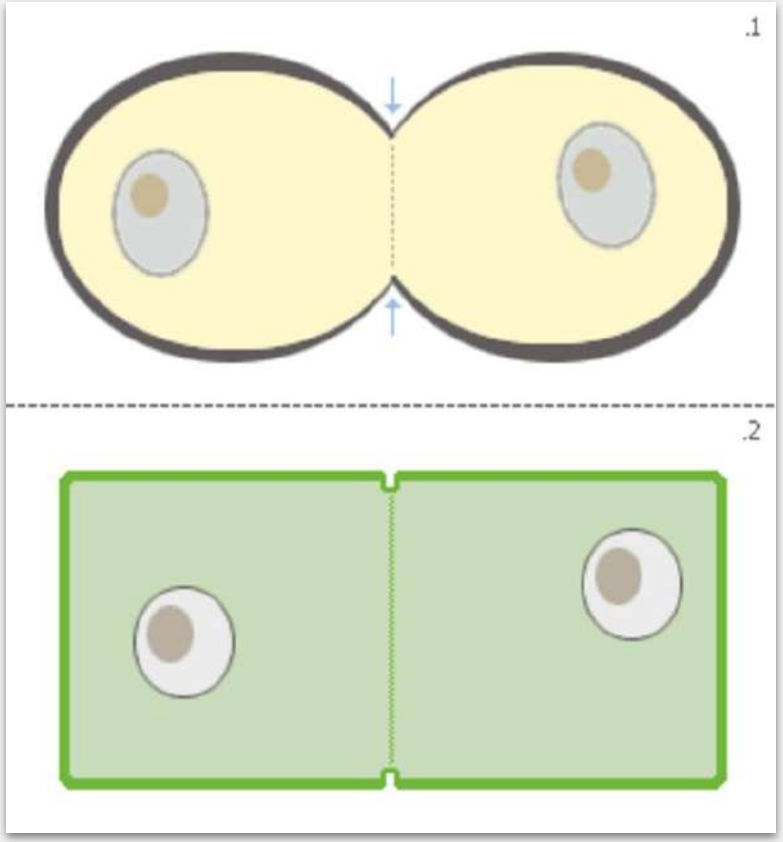
- ➔ **Sister chromatids** at opposite poles
- ➔ Spindle disassembles
- ➔ Nuclear envelope forms around each set of sister chromatids
- ➔ Nucleolus reappears
- ➔ **CYTOKINESIS** begins
- ➔ Chromosomes appear as chromatin



Cytokinesis

Cytokinesis

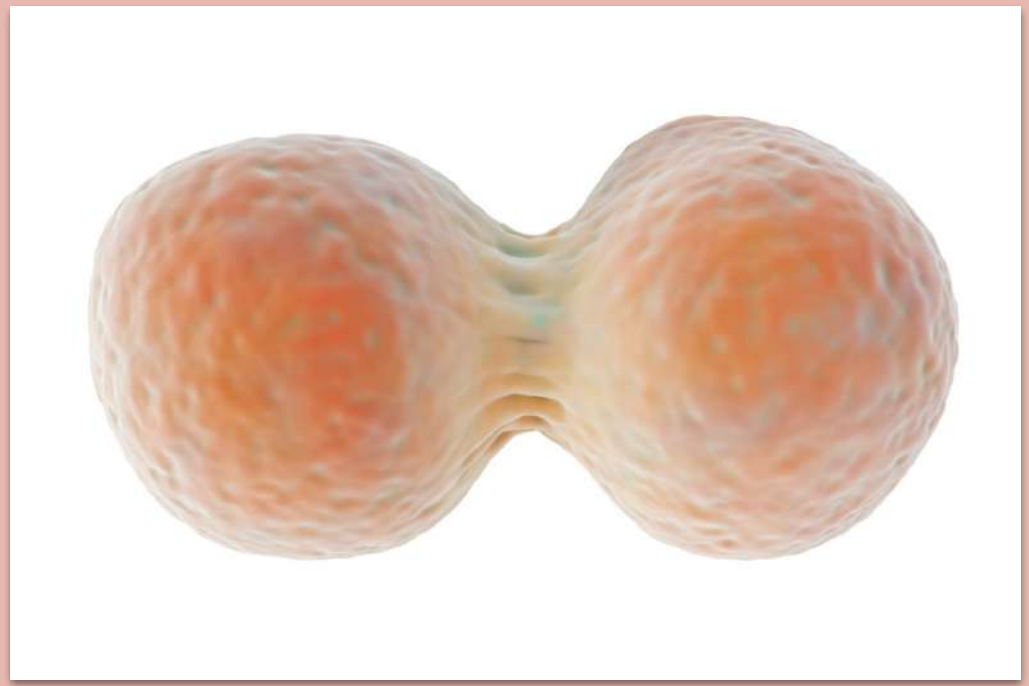
- ➔ Means **division of the cytoplasm**
- ➔ Division of cell into two, identical halves called daughter cells
- ➔ In **plant cells, cell plate f**orms at the equator to divide cell
- ➔ In **animal cells, cleavage furrow** forms to split cell



Daughter Cells

Daughter Cells

- Have the same number of chromosomes as each other and as the parent cell from which they were formed
  - ➔ **Identical** to each other, but smaller than **parent cell**
  - ➔ Must grow in size to become mature cells (G1 of Interphase)

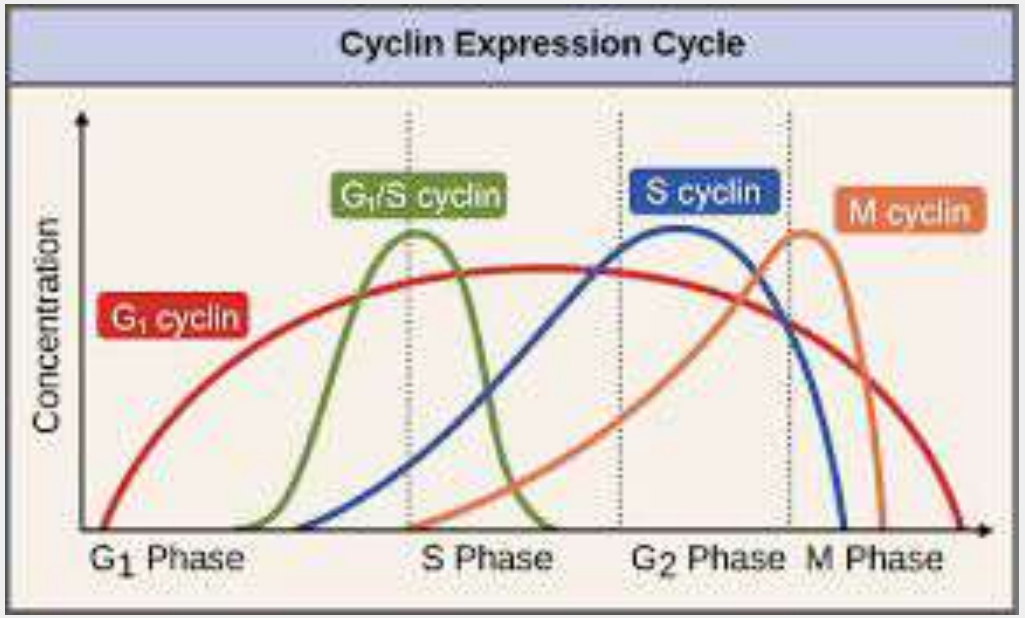


Control of the Cell cycle

Control of the Cell Cycle

- **Introduction**

1. **Importance of cell cycle regulation**
   - Proper control of the cell cycle is very important to maintain a balanced and healthy growth of cells.
   - When the cell cycle goes awry, it can lead to diseases like cancer and developmental disorders.
2. **Key players in cell cycle control**
   - Cyclins, CDKs, and cell cycle checkpoints are the main components that regulate the cell cycle.



Cyclins

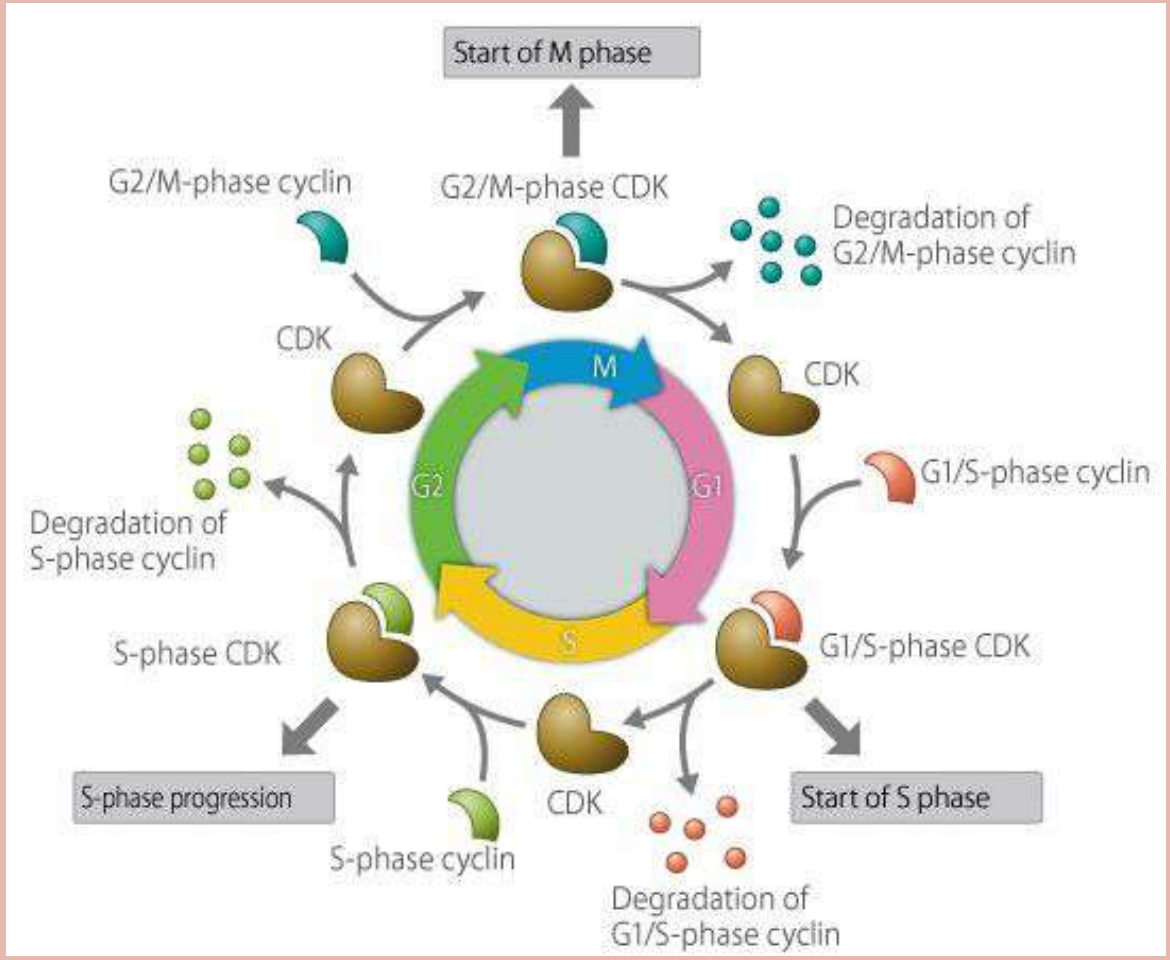
- **Cyclins**
  1. **Definition** and characteristics
     - **Cyclin-dependent proteins**
       a. Cyclins are special **proteins** that **regulate** the activity of other **proteins** called **CDKs**.
       b. They are **named cyclins** because their levels in the cell **go up** and **down** in a repeating **pattern** during the cell cycle.
     - **Regulatory proteins**
       a. **Cyclins** control the progress of the cell cycle by **binding** to and **activating** specific **CDKs**.
       b. They work like **helpers** for **CDKs**, enabling them to do their job of **adding phosphate molecules** to specific **proteins** involved in the cell cycle.
  2. **Function and role in cell cycle progression**
     - Activation of **cyclin-dependent kinases (CDKs)**
     - Cyclins **attach themselves** to **CDKs**, making them **active** and **ready** to work.
  3. **Formation of cyclin-CDK complexes**
     - **Cyclin-CDK combinations** add **phosphate** molecules to specific **proteins**, which helps move the cell through different phases of the cell cycle.

Cyclins cont'

4. **Regulation of cell cycle transitions**
   - **Cyclins** make sure that each **phase** of the **cell cycle** is **completed** before the cell **moves** on to the **next** phase.
5. **Specificity for different cell cycle phases**
   - **Different** cyclins are **active** at **different** times during the cell cycle, which **ensures** that each **phase** happens at the **right** time.
6. **Examples of cyclins and their roles**
   - **G1 cyclins (e.g., cyclin D)**
     - G1 cyclins help **cells move** from the **first growth phase (G1)** to the **DNA synthesis phase (S phase)** by activating certain CDKs.
   - **S-phase cyclins (e.g., cyclin E)**
     - **S-phase cyclins** help **start** the process of **copying** the **DNA** by activating specific CDKs.
   - **Mitotic cyclins (e.g., cyclin B)**
     - Mitotic cyclins help cells **transition** from the **growth phase (G2)** to the division phase (**mitosis**) by activating particular CDKs.

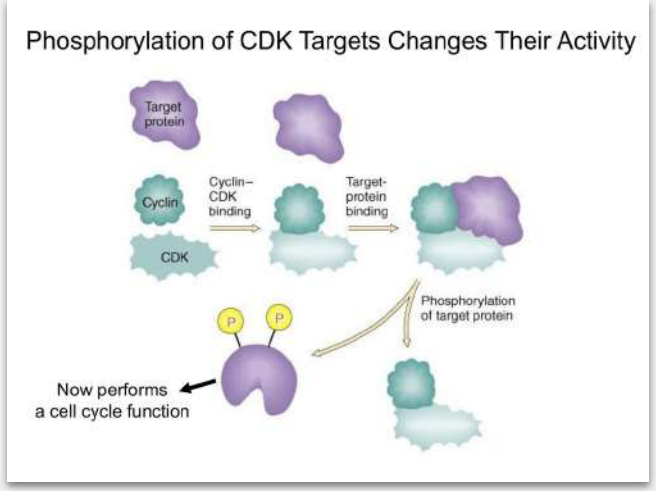
CDK's

- **Cyclin-Dependent Kinases (CDKs)**
  1. **Definition and characteristics**
     - **Special enzymes** - CDKs are **enzymes** that add **phosphate** molecules to other **proteins**, specifically on **serine** and **threonine** amino acids.
     - This process of adding phosphates is called **phosphorylation** and is important for controlling the cell cycle.
  2. **Association with cyclins**
     - CDKs work together with cyclins, and they need cyclins to become active.
  3. **Regulation by phosphorylation**
     - The activity of CDKs is **controlled** by **adding** or **removing phosphate** molecules on them.



CDK's cont'

4. **Activation and function of CDKs**
   - **Binding to cyclins**
     - CDKs attach themselves to cyclins to form active pairs.
   - **Phosphorylation and activation by CAK** (CDK-activating kinase)
     - CDKs need to be phosphorylated by another protein called CAK to become fully active.
   - **Substrate specificity and phosphorylation targets**
     - **CDKs add phosphate** molecules to specific proteins that are involved in controlling the cell cycle.
   - **Role in cell cycle progression**
     - CDKs help the cell move through different phases of the cell cycle by phosphorylating key proteins.
   - **Examples of CDKs and their roles**
     - **CDK4** and **CDK6** in **G1 phase**
     - **CDK4** and **CDK6**, when joined with **cyclin D**, help cells move from the first growth phase (**G1**) to the next phase.
     - **CDK2** in **S phase**
     - **CDK2**, along with **cyclin E**, starts the **DNA replication** process during the DNA synthesis phase (**S phase**).
     - **CDK1** in **G2** phase and **mitosis**
     - **CDK1**, when combined with **cyclin B**, helps cells transition from the growth phase (**G2**) to the division phase (**mitosis**).



Checkpoints

- **Cell Cycle Checkpoints**
  1. **Definition** and importance
     - **Special control points**
       - **Cell cycle checkpoints** are like checkpoints along the cell cycle, where the cell **stops** and **checks** if everything is going well **before** moving **forward**.
       - These checkpoints are **crucial** to ensure that the cell **divides** correctly and doesn't make **mistakes**.
  2. **Preventing cell cycle progression under unfavorable conditions**
     - Checkpoints **stop** the cell cycle if there are **problems** like **damaged DNA** or unfavorable conditions for growth.
     - This pause gives the cell time to fix the problems or make sure everything is ready before moving on.
  3. **Checkpoints**
     - **G1/S checkpoint**
       - **Role in assessing DNA integrity and growth conditions**
         - ★ The G1/S checkpoint checks if the DNA is intact and if the cell has the necessary conditions for growth before entering the DNA synthesis phase (S phase).
       - **Activation and inhibition of cyclin-CDK complexes**
         - ★ Certain proteins can either activate or stop the activity of cyclin-CDK pairs to pause the cell cycle at this checkpoint.

Checkpoints Cont'

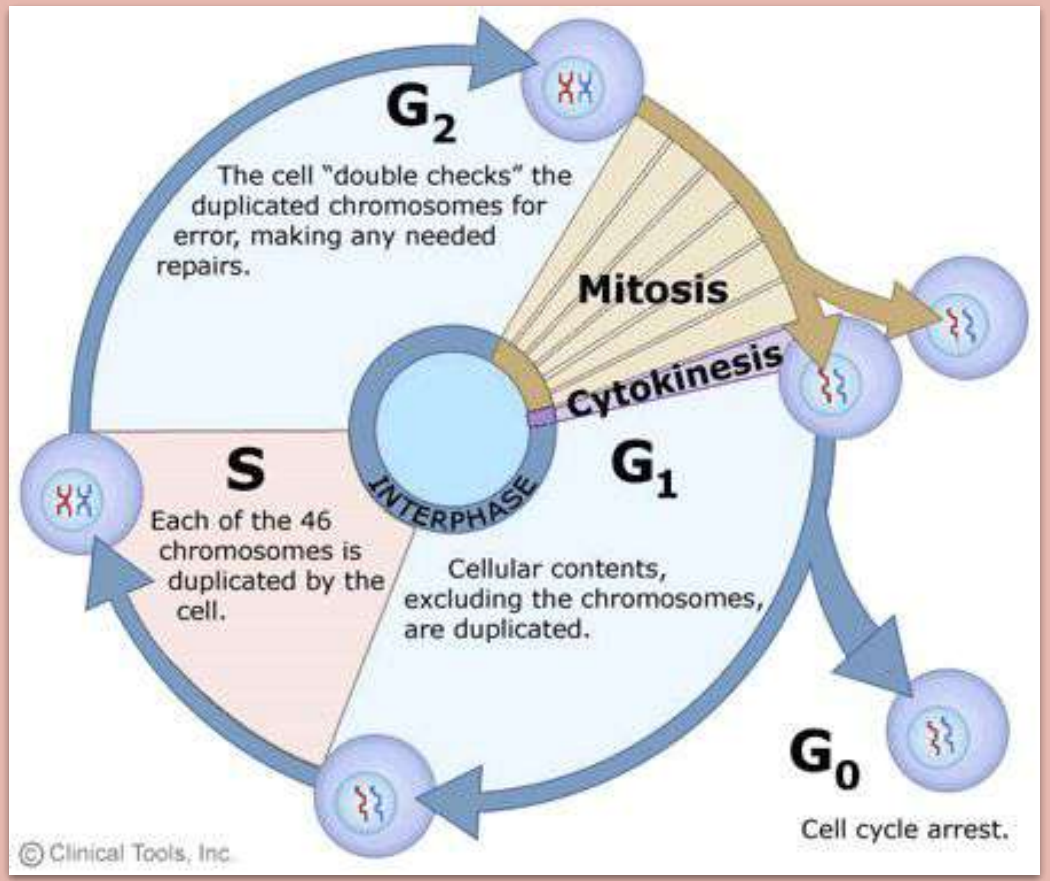
- **G2/M checkpoint**
  - **Role in DNA replication completion and DNA damage detection**
    - ★ The G2/M checkpoint makes sure that **DNA replication is finished** and **detects** any DNA **damage** before the cell enters the division phase (mitosis).
  - **Activation and inhibition of cyclin-CDK complexes**
    - ★ Special proteins can stop the activity of cyclin-CDK pairs to halt the cell cycle at this checkpoint.
- **Metaphase / Spindle assembly checkpoint**
  - **Role in monitoring chromosome attachment to the spindle apparatus**
    - ★ The spindle assembly checkpoint ensures that chromosomes are correctly attached to the structures called spindles during the division phase (mitosis).
  - **Delaying anaphase onset until all chromosomes are properly aligned**
    - ★ If chromosomes are **not correctly attached**, this checkpoint **stops** the cell from moving **forward** until everything is **properly aligned** to prevent errors.
- **DNA damage checkpoint**
  - **Role in detecting DNA damage and activating repair mechanisms**
    - ★ The DNA damage checkpoint senses any damage to the DNA and activates repair processes to fix it.
  - **Activation of cell cycle arrest or DNA repair pathways**
    - ★ This checkpoint can pause the cell cycle or initiate DNA repair processes to ensure the DNA is in good condition before continuing.

Cancer

Uncontrolled Mitosis:

- If mitosis is not controlled, unlimited cell division occurs causing cancerous tumors
- At **Checkpoint G_0** - The cell has a decision to make - keep replicating, go perform its function, or **Apoptosis**- Cell death. If the cell is beyond its normal replication cycle or has mutations and keeps dividing- Cancer.
- **Oncogenes** are special proteins that increase the chance that a normal cell develops into a tumor cell
- **What is Cancer?**
  - Cancer is essentially a **disease of mitosis** - the normal 'checkpoints' regulating mitosis are ignored or overridden by the cancer cell. Cancer begins when a single cell is **transformed**, or converted from a normal cell to a cancer cell.
  - Often this is because of a change in function or a **mutation** that occurs in one of several **genes** that normally function to control growth.

Cancer Continued



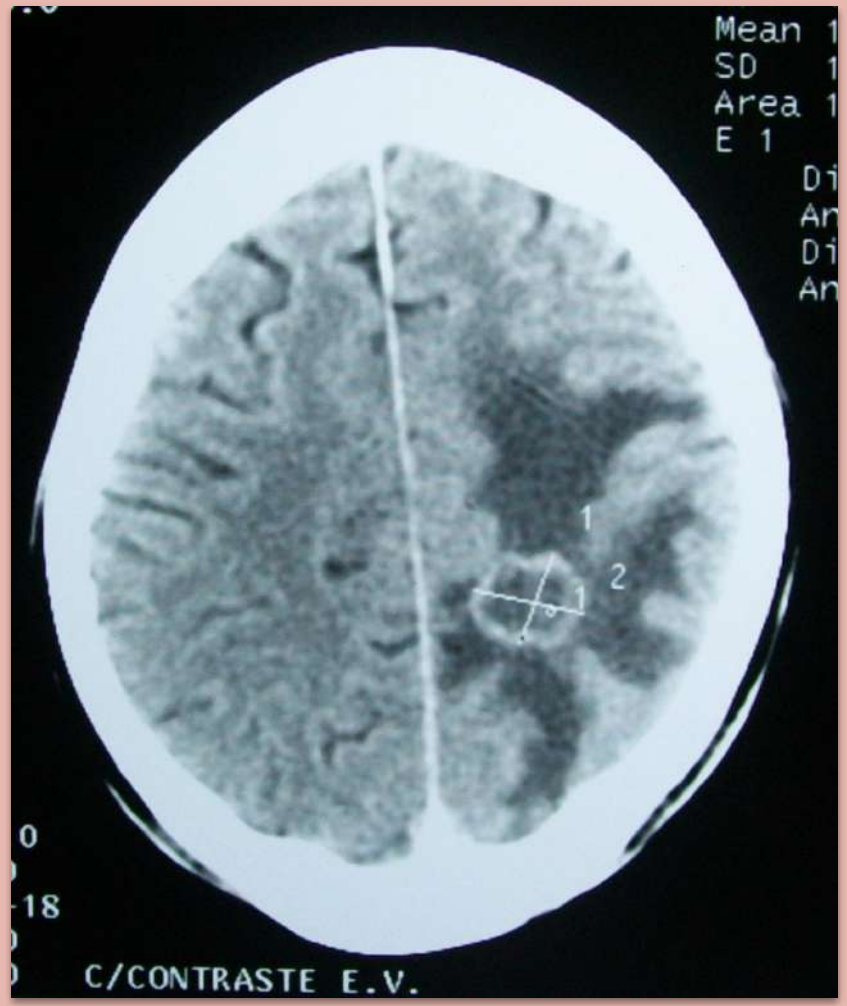
Examples:

- ➔ The **p53 gene, the** "guardian of the genome", usually functions to properly control the cell cycle. However, p53 is mutated in over 50% of all human cancers.
- ➔ **The BRCA-1 gene, the "Breast Cancer Gene"** normally functions to suppress tumor formation; but if a **gene** contains **mutations** such that BRCA1 does not work properly, tumor formation can begin (Note: mutations in this gene do not mean that a person will develop breast cancer, just that they have an increased risk for breast cancer).

Tumors

- Once these crucial **Cell Cycle genes** start behaving abnormally, cancer cells start to proliferate wildly by repeated, uncontrolled mitosis.
- **Tumors - Good Cells gone Bad...?** The cancer cells proliferate to form a mass of cancer cells called a tumor. As the tumor grows larger, it begins to release proteins from the cell to attract new blood vessel growth (this is called *angiogenesis*). At this point the tumor contains ~ 1 million cells and is about the size of a '*bb*'.

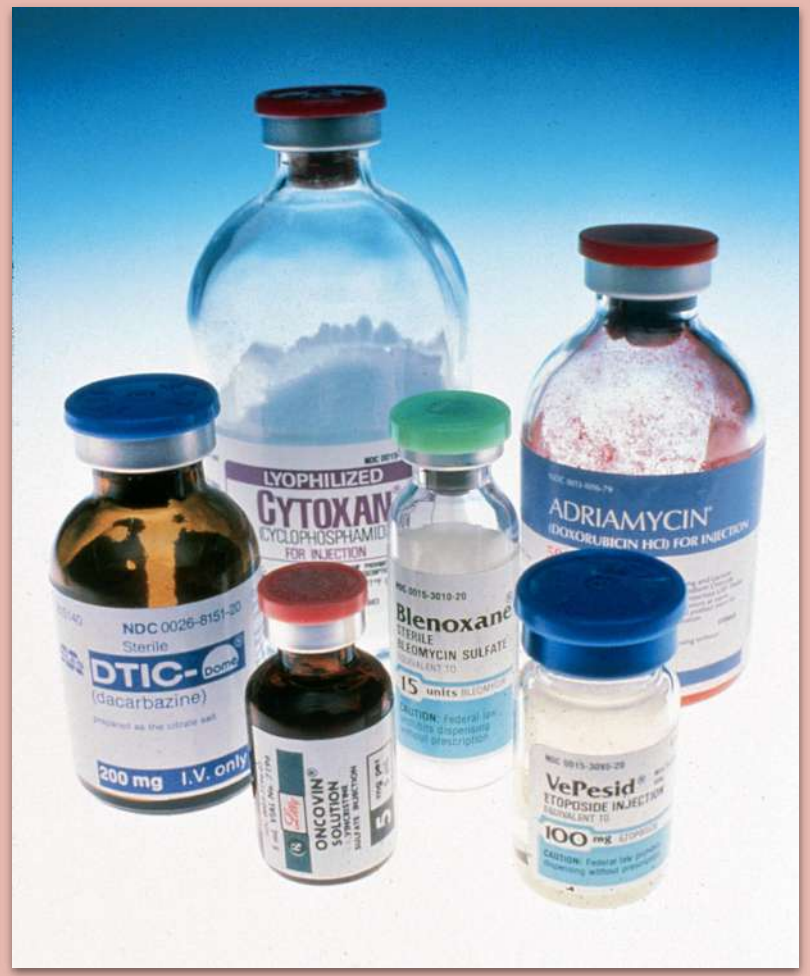
1) **Benign**: tumor cells remain at the original site. Can be removed surgically or killed by radiation, usually eliminating any further cancer development at that site.
2) **Malignant**: some tumor cells send out signals that tell the body to produce a new blood vessel at the tumor site. These cells not only have their own food and oxygen supply, they also have an avenue for escape to a new part of the body - through the new blood vessel and into the bloodstream. Cells that break away from the tumor begin to spread to surrounding tissues (via the bloodstream or lymph) and start new tumors = *metastasis*. Usually surgery is performed to remove the tumor, followed by radiation and chemotherapy.



Characteristics of Cancer

- Cancer cells are frequently **"immortal ":** whereas normal cells divide about 50 times and they die, cancer cells can go on dividing indefinitely if supplied with nutrients
- Cancer cells often have unusual numbers of chromosomes or mutations in chromosomes. Aging (production of toxic oxygen "free radicals"), exposure to toxins (like components of tobacco tar), mutagens (like ultraviolet light) all cause mutations in genes and cancer; but normal errors in DNA replication can lead transformation of the cell if they occur in a crucial gene.
- Cancer cells may also have an abnormal cell surface; instead of **"sticky "** to its neighboring cells, cancer cells tend to "round up" and break attachments to its neighbors cells, allowing for metastasis.
- Cancer cells ignore the usual density-dependent inhibition of growth in cell culture (or in body tissues), multiplying after contact with other cells are made, piling up until all nutrients are exhausted.

Cancer - Treatments

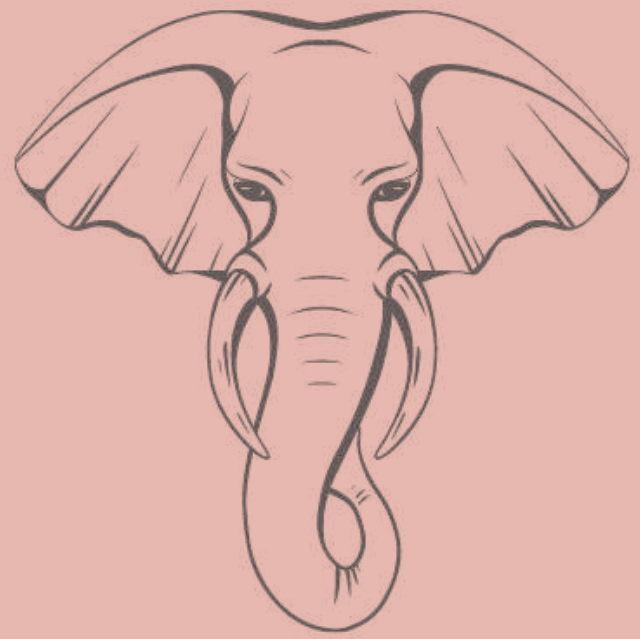


Stopping cancer cell growth:

- **Chemotherapy Drugs** stop DNA synthesis/ replication:
- Adriamycin and Cytoxan prevent DNA from unwinding properly,
- **5FU** inhibits incorporation of T nucleotides
- **Methotrexate and 5-MP** prevent cells from making nucleotides
- **ARA-C** is a C nucleotide "mimic" that gets incorporated and stops further DNA synthesis - No DNA replication, no new cancer cells!

The Cell Cycle - A Summary

Why	Growth & Repair
When	From fertilization until death
Where	Somatic/Body cells - skin, muscle, bone, tissues, etc…
Outcomes	2- Genetically Identical Daughter cells



Thank you!

Do you have any questions?
instructor@email.com
xxx-xxx-xxxx x-xxxx